Quantum-Chemical Simulation of ^{1}H NMR Spectra. 2.[†] Comparison of DFT-Based Procedures for Computing Proton−Proton Coupling Constants in Organic Molecules

Thomas Bally*,[‡] and Paul R. Rablen*,[§]

[‡]Department of Chemistry, University of Fribourg, CH-1700 Fribourg, Switzerland

[§]Department of Chemistry & Biochemistry, Swarthmore College, Swarthmore, Pennsylvania 19081-1397, United States

Ⓢ *Supporting Information*

ABSTRACT: The performance of 250 different computational protocols (combinations of density functionals, basis sets and methods) was assessed on a set of 165 well-established experimental ^{1}H−^{1}H nuclear coupling constants ($J_{H−H}$) from 65 molecules spanning a wide range of "chemical space". Thereby we found that, if one uses core-augmented basis sets and allows for linear scaling of the raw results, calculations of only the Fermi contact term yield more accurate predictions than calculations where all four terms that contribute to $J_{H−H}$ are evaluated. It turns out that B3LYP/6-31G(d,p)u+1s is the best (and, in addition, one of the most economical) of all tested methods, yielding predictions of $J_{H−H}$ with a root-mean-square deviation from experiment of less than 0.5 Hz for our test set. Another method that does similarly well, without the need for additional 1s basis functions, is B3LYP/cc-pVTZ, which is, however, ca. 8 times more "expensive" in terms of CPU time. A selection of the better methods was tested on a probe set comprising 61 $J_{H−H}$ values from 37 molecules. In this set we also included five molecules where conformational averaging is required. The rms deviations were better than or equal to those with the training set, which indicates that the method we recommend is generally applicable for organic molecules. We give instructions on how to carry out calculations of ^{1}H chemical shifts and $J_{H−H}$ most economically and provide scripts to extract the relevant information from the outputs of calculations with the Gaussian program in clearly arranged form, e.g., to feed them into programs for simulating entire ^{1}H NMR spectra.
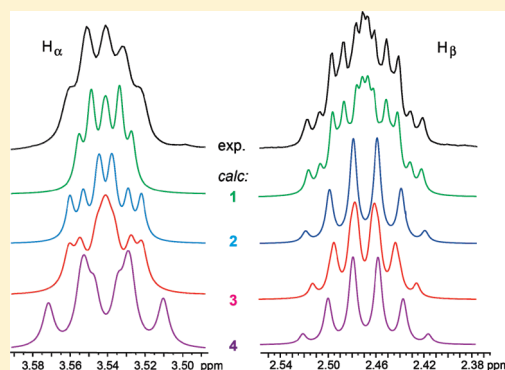
■ INTRODUCTION

Probably no method of identifying and characterizing organic compounds is more powerful or more ubiquitous than nuclear magnetic resonance (NMR) spectroscopy. Although many magnetic nuclei are available, and numerous powerful and sophisticated 1-, 2-, or higher dimensional techniques have been developed to analyze and disentangle the information contained in NMR spectra, the ordinary 1-dimensional proton spectrum is usually the first and often remains the only NMR spectrum that is measured for a compound. The primary information contained in ^{1}H NMR spectra consists of chemical shifts and proton−proton coupling constants ($J_{H−H}$). Over the years, organic chemists have acquired a great deal of empirical knowledge relating the typical values of these quantities to molecular and (to some extent) electronic structure, and by using this knowledge they have become highly adept at deducing structures from their spectra.[1,2]

Nonetheless, such empirical relationships are often inadequate for the purpose of distinguishing subtle differences between similar structures, such as diastereomers, or for the analysis of highly unusual structures that fall outside the realm within which the empirical relationships were derived. In practice, it is often necessary to choose between a limited set of candidate structures that are expected to have measurably different NMR spectra, but where the nature of the differences cannot be predicted on an empirical basis. In such cases, it has often proven effective to use electronic structure theory, and particularly density functional theory, to predict the chemical shifts and/or the coupling constants of the candidate structures. Frequently, the predictions for one structure will match the experimental values far better than the predictions for the other structures, and in this way an assignment can be made with considerable confidence.

A rich literature addressing this approach has developed over the past decade. Far too many examples abound to list them comprehensively here, and so we are left to cite a few recent reviews and topical papers that provide a more thorough overview of the extensive work that has been performed in this area.[2−17]

The feasibility of predicting NMR chemical shifts and coupling constants by means of density functional calculations has

thus been thoroughly established by now, and additional persuasive examples continue to appear regularly in the literature. What has so far been lacking, however, is a broad comparison of the performance of various available methods with regard to the question of which procedures provide the best agreement with experiment at the lowest computational cost for a set of organic compounds that represents a large part of "chemical space". Insofar as the practice of predicting ¹H NMR spectra using electronic structure theory becomes commonplace even among nonspecialists, as we believe it should, it would certainly behoove practitioners to know what combinations of methods, functionals, basis sets, etc., provide the best balance between cost and accuracy.

We have previously addressed the same issue with regard to the computation of proton chemical shifts;[18] here, we turn our attention to the more recently developed methodology for computing coupling constants, focusing once again on proton–proton couplings, J_{H-H}, in an effort to serve the large community of chemists who measure and interpret the countless ¹H NMR spectra that are recorded every day.

It is common practice among organic chemists to predict and explain the coupling of *vicinal* protons on the basis of the Karplus equation, $^{3}J_{H-H}(\phi) = A\cos^2\phi + B\cos\phi + C$, which relates the coupling of two protons to the dihedral angle ϕ of the two X–H bonds.[19] To put this relation into practice, values for the empirical parameters A, B, and C must be determined, and these depend on the nature of the two atoms to which the two hydrogen atoms are bonded, on the substituents, and on the valence angles on these atoms. Thus, the Karplus equation is usually only valid for a specific set of circumstances, where it may then yield very accurate predictions. An excellent example are the furanoses where Altona et al. have elaborated a whole apparatus to extract information on the major conformers from complicated NMR spectra, on the basis of the Karplus equation.[20]

In contrast, quantum chemistry makes no assumptions with regard to the chemical environment and is thus apt to make equally valid predictions for nuclear couplings in all compounds. Today, most standard quantum chemical programs allow the calculation of chemical shifts and nuclear coupling constants,[7] so the tools to simulate entire NMR spectra are in principle available. Nevertheless, these tools still seem to see very limited use in general practice, probably because the activation barrier for engaging in quantum chemical calculations is still too high for most practicing organic chemists. We hope that this paper will contribute to lowering this barrier and lead to a wider application of the great tools that theoreticians have developed for us.

■ THEORETICAL BACKGROUND

Although the focus of this paper is on the practical applicability of different methods to calculate J_{H-H} rather than on the theory behind these calculations, some background knowledge is helpful to understand why some methods are better than others and why the methods that are commonly advocated by the theoreticians who develop them are often unnecessarily expensive if and when one targets exclusively proton–proton couplings. Thus, we will review below a few basic elements of the theory, while inviting readers who have no interest at all in this topic to skip this section, which is based on recent reviews.[6–8]

NMR spectroscopy traces the interactions of the magnetic moments of nuclei with non-zero spin (e.g, ¹H, ¹³C) among themselves and with those of the electrons which surround them

in molecules. In an external magnetic field, which leads to the splitting of the sublevels created by the above interactions, these become spectroscopically palpable because transitions between these split levels can be induced by electromagnetic radiation in the radiofrequency range.

Apart from the information in the *chemical shifts* of the individual protons, NMR spectra show the *couplings* between the magnetic moments of different nuclei which are mediated by their interactions with the magnetic moments of the electrons and thus lead to splittings of lines in the NMR spectra into patterns that are indicative of the kind and the number of nuclei whose interactions manifest themselves (or can be resolved). In ¹H NMR spectra these patterns can be very complicated and their disentanglement may require much experimental effort and may be greatly aided by reliable predictions of the individual coupling constants.

Nuclear spin–spin coupling constants can be expressed as second derivatives of the energy with regard to the magnetic moments of the two interacting nuclei. As these moments are vectors, the couplings between them are described by 3 × 3 tensors. However, in measurements of isotropic samples, only the traces of these tensors, i.e., the average values of the three diagonal elements, are of relevance, so we will limit ourselves to those.

The coupling of nuclear spins may be regarded as involving different mechanisms, the contributions of which are evaluated separately in quantum chemical calculations. The first of these contributions represents the interactions of the nuclear magnetic moments with those created by the *movement* of the electrons around them, the so-called spin–orbit (SO) coupling; the operator that describes this contribution has a diamagnetic (DSO) and a paramagnetic (PSO) component. The second contribution describes the interaction of the electron's *spins* with the nuclear magnetic fields, the so-called spin hyperfine interaction. Accounting for this effect involves again two terms, one of which describes the interaction *at the position of the nucleus* (the Fermi contact or FC term,) while the other represents the remaining part (the spin–dipole or SD operator).

The DSO contribution is the easiest to calculate because it can be computed simply as the expectation value of a one-electron operator acting on the ground-state wavefunction. The often dominant FC term expresses the perturbation of the (closed-shell) wavefunction by the presence of a magnetic nucleus, which causes this wavefunction to have different α- and β-densities at this nucleus.[21] To model this effect requires admixture of triplet configurations to the ground state, which is technically achieved by solving a linear response equation for each magnetic nucleus.[22]

The other two terms, which also contribute to the electronic spin polarization, formally imply sums over terms involving all excited states (singlet in the case of the PSO, triplet in the case of the SD term), but the calculation of these interactions implies the solution of ten different response equations for each nucleus (compared for example to three for the entire molecule in the calculation of chemical shifts), which indicates that the full evaluation of coupling constants is a much more involved procedure than that used to calculate chemical shifts.

Although the relative weights of the four contributions to the coupling between pairs of nuclei vary depending on the nature of the nuclei and whether the are geminal, vicinal, or separated by bonds of different types, it is often stated in theoretical papers that none of these terms ever dominates to the extent that the

others may a priori be neglected; i.e., any quantitative prediction would be expected to require the evaluation of all four of them. However, for proton couplings the *sum* of the two SO and the SD contributions is often small compared to the FC term, so one may argue that lower levels of theory may be used in calculating the former terms, or even that these terms may be neglected, propositions which we will examine in the perspective of the particular case of J_{H-H}.

It was realized quite early that the normal (restricted) Hartree−Fock (RHF) method fails abysmally for nuclear spin couplings, and it was recently demonstrated that this is mainly due to triplet instabilities[23] and that (static) electron correlation must be accounted for to obtain reasonably reliable prediction of spin−spin coupling constants. Thus, the variational configuration interaction (CI) or multiconfiguration self-consistent field (MCSCF) methods may be used, but nowadays, many-body perturbation theory, usually within the framework of coupled cluster theory, is used in most ab initio calculations of coupling constants which have thus reached an impressive level of accuracy.[3] However, such calculations are too expensive to be applicable to molecules such as practicing organic chemists typically deal with.

Luckily, Kohn−Sham (KS) density functional theory (DFT), in particular in its original form (i.e., the local density approximation), suffers to a much smaller extent from triplet instabilities than RHF does (although the problem may still manifest itself in unusual bonding situations[24]). Consequently, most predictions of NMR spectra for medium to large organic molecules by quantum chemical methods rely on one or the other flavor of KS-DFT. Admitting a part of HF exchange, as it is done in the hybrid exchange functionals, enhances the possibility for triplet instabilities, but these methods produce much more accurate results and are, therefore, preferred over "pure" density functionals. In particular, variants of the B3LYP functional have become popular in attempts to simulate NMR spectra with similar accuracy as the much more demanding coupled-cluster calculations.

However, it was also noted that, to accurately predict nuclear coupling constants, rather large basis sets are needed, in particular due to the requirement that, for the evaluation of the FC term (which is proportional to the electron density at the nucleus), the density at the nucleus must be modeled as faithfully as possible. Thus, special basis sets were developed for the calculation of nuclear spin−spin coupling constants, and the dependence of the results on basis sets was assessed and analyzed in detail.[25] Thereby it became apparent that decontracting the core shells (1s AOs in organic molecules) and adding additional tight functions for the purpose of calculating the FC term, while standard basis sets are used to evaluate the other contributions, may go a long way toward a systematic improvement of the predictions.[26−28] Such a "mixed basis set" option has been implemented in the latest release of the Gaussian program,[29] and we will examine to what extent this option helps to improve predictions of J_{H-H}.

Actually, most of the time practitioners of NMR spectroscopy are not interested in the couplings between *all* the nuclei (or even all the protons) in a molecule. Thus, it would be more economical to augment the basis set only on those atoms that are involved in spin−spin couplings of interest, a possibility that was exploited extensively by Kirvdin et al.[30] and will also be examined here.

Finally, a factor that can affect NMR parameters in general is the presence of large-amplitude vibrations which by averaging may in some cases lead to deviations of 5−10% from the values computed at equilibrium geometries.[31−33] However, as

calculations that account for vibrational averaging are inapplicable to large molecules, we will disregard these effects in our study.

■ METHODS

Test and Probe Set. It is our purpose to gauge the performance of coupling constant calculations per se, without the intrusion of complicating factors such as substantial experimental error or uncertainty about the conformational makeup of molecules. In this perspective, we constituted a test set composed of 165 J_{H-H} from 66 relatively small organic molecules each having a single, well-defined conformation,[34] selected primarily from a set of NMR texts that provide listings of coupling constants.[1,35−37] We note that in the course of the work it became evident that some of the couplings reported in such textbooks and reviews are probably erroneous. In some of these cases, the primary literature revealed correct values, but in others we had to remeasure the coupling constants. The molecules in the test set are depicted in Scheme 1, while the couplings that were taken into account, the source of these data, and other details are provided in the Supporting Information.

Although we attempted to configure our test set such that it covers a representative part of the "chemical space", we wanted to ascertain that the methods we advocate eventually for the calculations of J_{H-H} are not bound to that choice of compounds, for example, by the empirical scaling that we derived from the test set (see below). Thus, we constituted a "probe" set of molecules carrying other functionalities and showing different geometrical arrangements than those of the molecules in the test set. This set comprises 37 molecules and 61 J_{H-H} values and includes five cases where Boltzmann-weighted averaging of multiple conformations is required.

Empirical Scaling. Initially, we directly compared computed coupling constants to experimental values. However, linear scaling has often proven effective to improve computational prediction of various

Scheme 1. Test Set of Molecules Used in Evaluating Scaling Factors for Calculated J_{H-H}
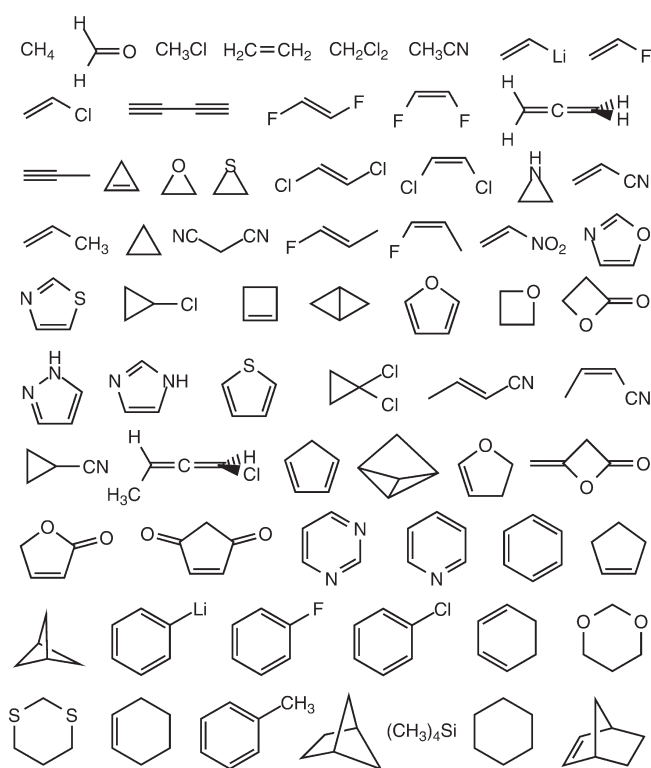
spectroscopic properties at no computational cost. Certainly, this approach is firmly established for predicting vibrational frequencies,[14,38] and it is also widely used for the calculation of chemical shifts.[18,39] Therefore, we also assessed the results of using a least-squares linear fit, either with a non-zero intercept or with the restriction for the regression line to pass through the origin. In general, we found that, for the methods with the best performance, there was no significant difference between these two types of fits. As it is preferable to reduce the number of adjustable parameters in empirical scalings, and since there is no theoretical justification for a nonzero intercept,[40] we have taken as our general "quality of fit" parameter the root-mean-square (rms) deviation between experiment and the calculated values *after linear scaling* by the single multiplicative parameter obtained from the least-squares fit restricted to pass through the origin.

Density Functional Methods and Basis Sets. We chose to include in our comparison a broad swath of density functional methods. The popular B3LYP functional has enjoyed extensive use for the calculation of NMR properties and was therefore subjected to particular scrutiny, as was also the WP04 functional developed by Cramer and co-workers for the explicit purpose of computing proton chemical shifts.[41] These two functionals were used in combination with nine different double- and triple-ζ basis sets from the Pople or the Dunning families and applied to structures optimized at the B3LYP/6-31G(d) level. These combinations gave rise to 18 methods that were then each tried in four configurations: with and without geometry reoptimization at the level used to calculate the couplings and with or without simulation of the solvent by the SCRF polarizable continuum model implemented in Gaussian 09 [scrf(solvent = chloroform)]. This gives a total of 72 methods.

To accurately calculate the Fermi contact terms, which tend to dominate J_{H-H}, requires special basis sets (see the Theoretical Background section). Deng and Frisch have proposed a systematic and general approach for uncontracting and augmenting the core basis functions (usually four compact 1s functions are added to each H-atom).[28] This procedure is implemented in the Gaussian 09 program[29] where it is invoked with the "mixed" option. We will tag these "mixed" basis sets by appending "u+1s" (for "uncontracting and augmenting by extra compact 1s functions"). All of the 72 methods described above were carried out both with and without using this option, for a total of 144 procedures that were applied to our entire test set of 66 molecules comprising 165 proton–proton couplings.

The above exploration led to the conclusion that using the "mixed" option indeed improves the root-mean-square deviation between measured and calculated J_{H-H} but that this measure was very little affected by the inclusion of solvent, in contrast to the calculation of chemical shifts.[18] Also, reoptimization of the geometry with larger basis sets proved to change the calculated couplings imperceptibly in most cases. On the basis of these observations, other functionals were explored only by the gas-phase, single-point "mixed" procedure and with a subset of basis sets that had appeared promising from the B3LYP and WP04 studies: 6-31G(d), 6-31G(d,p), 6-311G(d,p), cc-pVDZ, and cc-pVTZ. The functionals studied in this manner were B3P86, B3PW91, B97D, BHandH, BHandHLYP, BMK, CAM-B3LYP, M06, M06L, M062X, mPW1PW91, O3LYP, PBE1PBE, PBEh1PBE, TPSSh, VSXC, wB97XD, and X3LYP. These combinations gave rise to 90 additional methods.

A closer examination of basis set effects was also carried out specifically with the B3LYP functional, with particular attention to adding functions on the hydrogen atoms, using the mixed option and single-point gas-phase calculations. The additional basis sets were 6-31G(d,3dp), 6-311G(d), 6-311G(2d,p), 6-311G(2d,2p), 6-311G(df,2pd), 6-311G(df,3pd), 6-311G(2df,p), 6-311G(2df,2p), 6-311G(2df,pd), 6-311G(2df,2pd), 6-311G(2df,3pd), 6-311G(3d,2p), 6-311G(3df,3pd), 6-311++G(df,2pd), 6-311++G(df,3pd), 6-311++G(2df,3pd), and 6-311++G(3df,3pd).

All told, 251 different combinations of density functional, basis set, basis set augmentation in the core or not, and with or without geometry reoptimization were thus investigated.

Calculations of Different Terms That Contribute to J_{H-H}. The (comparatively straightforward) calculation of Fermi contact (FC) terms has been possible for a long time. In contrast, the equations required to calculate the other three terms that contribute to nuclear spin couplings have been coded more recently and have therefore seen less practical use. Thus, early efforts in computational modeling of NMR spectra relied on calculations of the FC terms only, which tend to dominate the J_{H-H}. For instance, Bagno et al. have worked extensively and very successfully on the prediction of ^{1}H NMR spectra of moderately complex organic molecules, based on calculations of only the FC terms, using mostly the cc-pVTZ basis set throughout (i.e., without augmenting basis set on H by compact functions, as described above).[4,5,42,43]

As computation of the FC terms is considerably more economical than that of all four terms contributing to nuclear spin coupling (see the Theoretical Background section), we deemed it appropriate to examine whether one could get away, for the particular case of calculation of J_{H-H}, with neglecting these other terms without too much loss in accuracy (calculations that we will call "FConly", in contrast to those of all four terms that we will call "Jtotal" calculations), and to see whether decontracting and augmenting the H(1s) basis set helps to improve the accuracy in this case. As the standard G09 output for a calculation of coupling constant lists all four terms, this study required no additional calculations, though it formally added another 251 methods to our slate.

■ RESULTS AND DISCUSSION

The full statistics for all the methods outlined in the above section (Methods) appear in the Excel spreadsheet that is provided, next to a text file with the raw data, as part of the Supporting Information. Here we will limit ourselves to a presentation of selected aspects of these statistics to highlight one or the other facet of our study.

Figure 1 depicts a representative comparison of experimental and calculated J_{H-H}, including the best-fit line, for the method that we finally found to be the best one in terms of cost/performance: gas-phase B3LYP, with the 6-31G(d,p) u+1s basis set, using only the Fermi contact term. The slope of the best-fit line (passing through the origin) is the single-parameter scaling factor to be applied to the computed coupling constants. The agreement between calculation and experiment is rather good, with the difference almost always less than 1.0 Hz. The red dots represent the only two cases, out of 165, where the difference exceeds 1.5 Hz, and the blue dots represent the only five cases for which the difference lies between 1.0 and 1.5 Hz.

Density Functionals. Different exchange and correlation functionals were explored with a set of five basis sets of a reasonably varied nature that had provided good performance at modest cost when used with B3LYP: 6-31G(d), 6-31G(d,p), 6-311G(d,p), cc-pVDZ, and cc-pVTZ. Since both geometry reoptimization and inclusion of solvent made little difference in the case of B3LYP (see below), the calculations for exploring other functionals were all performed in the gas phase, and using the B3LYP/6-31G(d) geometries. However, the basis sets were uncontracted and augmented with compact 1s functions ("u+1s"), since with B3LYP this option was often found to provide significant improvement in accuracy, especially with smaller basis sets such as 6-31G(d).

Table 1 summarizes rms deviations between measured J_{H-H} and the calculated Fermi contact (FC) terms or total coupling
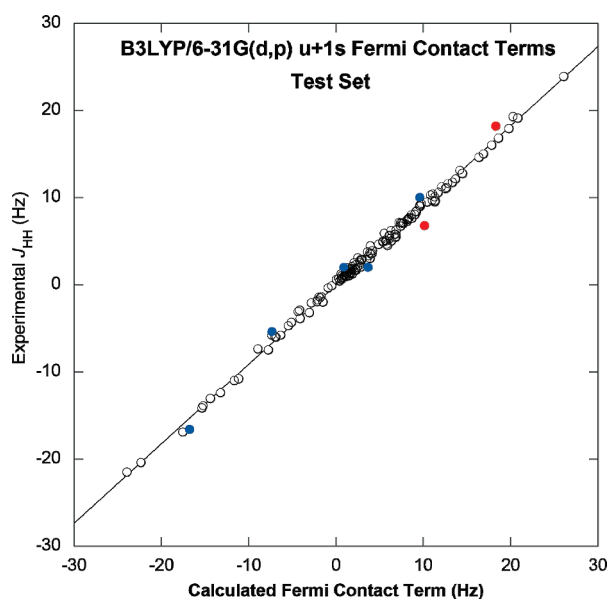
Figure 1. Plot of B3LYP/6-31G(d,p)u+1s calculated Fermi contact terms against the experimental coupling constants from the test set (166 total coupling constants). The line represents a least-squares fit restricted to pass through the origin and has a slope of 0.912. The solid red circles represent the two cases where experiment and (scaled) calculation differ by more than 1.5 Hz (bicyclo[2.1.1]hexane 4-bond W-coupling, 6.8 Hz expt vs 9.23 Hz calcd; bicyclo[1.1.1]pentane, transannular coupling, 18.2 Hz expt vs 16.68 Hz calcd). The solid blue circles represent the five other cases where experimental and (scaled) calculation differ by more than 1.0 Hz (dihydrofuran, alkene vicinal coupling, 2 Hz expt vs 3.35 Hz calcd; propiolactone, geminal coupling alpha to carbonyl, −16.6 Hz expt vs −15.29 Hz calcd; bicyclo[2.1.1]hexane geminal, −5.4 Hz expt vs −6.69 Hz calcd; bicyclo[1.1.1]pentane, 4-bond W-coupling, 10 Hz expt vs 8.75 H calcd; aziridine geminal coupling, 2 Hz expt vs 0.83 Hz calcd). The point for formaldehyde (40.7 Hz expt, 39.94 Hz calcd) has been omitted, since including it would compress all the other points on the plot substantially.

Table 1. Average RMS Deviations between Measured and Calculated J_{H-H} with Different Density Functionals (with or without Single-Parameter Scaling), Using the Following Five Basis Sets: 6-31G(d), 6-31G(d,p), 6-311G(d,p), cc-pVDZ, and cc-pVTZ All Augmented with the u+1s Option

	rmsd			
functional	Jtotal[a]	FC only[b]	Jtotal[a], scaled	FC only[b], scaled
B3LYP	0.93	0.98	0.70	0.51
X3LYP	1.02	1.08	0.72	0.53
BMK	1.50	1.62	0.83	0.64
B3P86	0.90	0.74	0.88	0.66
M062X	0.90	0.81	0.83	0.69
O3LYP	0.97	0.89	0.91	0.70
CAM-B3LYP	1.15	1.19	0.88	0.71
B3PW91	1.05	0.96	0.98	0.78
WB97XD	1.13	0.80	1.06	0.78
WP04	1.81	1.92	1.03	0.86
PBE1PBE	1.22	1.17	1.09	0.90
B97D	1.34	1.02	1.17	0.92
PBEh1PBE	1.28	1.23	1.13	0.94
mPW1PW91	1.38	1.37	1.16	0.97
BHandH	1.47	1.44	1.32	1.15
TPSSh	1.74	1.96	1.23	1.23
BHandHLYP	2.67	2.78	1.57	1.44
VSXC	1.90	1.72	1.85	1.63
M06L	5.85	5.80	3.78	3.60
M06	5.47	5.42	3.89	3.73

[a] Calculation of total coupling constants. [b] Calculation of Fermi contact terms only.

constants, respectively, with or without linear scaling, and averaged over the results obtained with the above five basis sets (for a given functional the rms deviations generally do not vary by more than 0.10 Hz from one basis set to another; therefore, averaging in this manner provides a reasonable, single measure of the performance of a functional).

The methods are listed in order of increasing rms deviation for the scaled FC term, i.e., in order or decreasing performance. In fact, this order does not depend significantly on whether one accounts for all terms that contribute to the coupling, or only the FC term (see the next section), and on whether one uses the scaled or the unscaled values. Five functionals offer performance notably better than the others: the four conceptually similar B3LYP, X3LYP, O3LYP, and B3P86 functionals, all of which contain three empirical parameters, and the M062X method. After scaling, the BMK and CAM-B3LYP methods are also on that list, while most other functionals yield predictions with rms deviations that are generally 0.3 to 0.5 Hz larger than those for the best functionals. Some functionals at the bottom of the list perform much more poorly.

If linear scaling is applied, the B3LYP and X3LYP functionals offer the best performance, both in Jtotal and FConly calculations. As the B3LYP functional has been shown to work well in predicting a wide variety of properties, this lends confidence that

the good J_{H-H} values obtained with this functional are not the result of a coincidence. We thus conclude that there is no compelling reason to use anything other than the B3LYP functional, a choice with which most people probably feel most comfortable, anyway.

The point about the generality of B3LYP is illustrated in reverse by the surprisingly poor performance of some of the functionals parametrized for specific purposes. The M06 and M06L functionals were developed with the goal of providing accurate energetics for compounds containing transition metals, a field of application where these functionals excel.[44] Conversely, they are remarkably poor at predicting proton coupling constants, and linear scaling does not overcome this deficiency (interestingly, the more generally applicable M062X functional is not afflicted by this problem). The meta-GGA functionals, TPSSh and VSXC, are also notably poor for the present purposes. Even the WP04 functional, which was developed specifically for the purpose of computing proton NMR chemical shifts, and performs exceedingly well for that purpose, yields rather mediocre proton NMR coupling constants. Thus, even parametrizing a functional for one proton NMR spectroscopic property can hamper its ability to calculate another such property.

Basis Sets. With the above conclusions in hand, we proceeded to explore *basis set effects* in more detail using the B3LYP functional. If one calculates all four components that contribute to the coupling of the proton's spins in organic molecules ("Jtotal"), which is the default procedure in most modern

quantum chemical programs that allow calculation of J_{H-H}, the results generally show the expected improvement if one increases the basis set, irrespective of whether one decontracts and augments the core functions or not (the trend is, however, more consistent if that option is invoked). Thus, additional and higher angular momentum polarization functions on heavy atoms are helpful, although the improvement decreases with successive additions. Surprisingly, additional polarization functions on hydrogen, beyond one set of p functions (which is needed), make almost no difference. Diffuse functions seem to make little difference one way or the other. The best overall agreement with experiment, at an rms deviation of 0.53 Hz, comes from the (very expensive!) calculations with one of the largest basis sets we have tried, 6-311++G(3df,3pd).

However, if one regards (or calculates) only the Fermi contact terms ("FConly"), the choice of basis set seems to make less of a difference, and the changes are less systematic, unless the core functions are augmented. Thus, in contrast to the full calculations discussed above, adding polarization functions on H (i.e., going from the 6-31G(d) to the 6-31G(d,p) basis set) has no effect on the rms deviation. On the other hand, adding an extra shell to the valence functions is beneficial: on going to the 6-311G(d,p) basis set the rms deviation drops from 0.84 to 0.63 Hz (similarly, the rms deviation drops from 0.99 to 0.51 Hz on going from cc-pVDZ to cc-pVTZ). Surprisingly, in this case, adding diffuse functions may cause the predictions to *deteriorate*: going from 6-31G(d,p) to 6-31++G(d,p) *increases* the rms deviation from 0.84 to 0.94 Hz, and going from cc-pVTZ to aug-cc-pVTZ increases it from 0.51 to 0.65 Hz. On the other hand, adding diffuse functions to the 6-311G(d,p) basis set *reduces* the rms deviation by 0.08 Hz, whereas the corresponding change has no effect in calculations with the cc-pVDZ basis set.

Particularly worth noting is the exceptional accuracy that is achieved with the cc-pVTZ basis set (rms deviation = 0.51 Hz), which had been used very successfully by Bagno et al. in their predictions of J_{H-H} in ^{1}H NMR spectra of natural products, based on calculations of the FC terms only.[4,5,42] Surprisingly, in calculations with this particular basis set only, augmenting it with additional core functions does *not* improve the results, which seems to indicate that some fortuitous (but apparently rather systematic) cancellation of errors is at work in this case.

With all other basis sets, decontracting and augmenting the 1s part of the basis set leads to significant enhancement of the agreement between calculations and experiment and eliminates the erratic behavior on "improving" the basis sets. Actually, the calculated FC terms calculated with this option depend very little on the valence part of the basis sets, which is perhaps not surprising, because FC terms depend only on the electron density at the nucleus which is not much affected by the availability of functions that are geared to optimally reproduce valence electron densities. We explored many different combinations of polarization and diffuse functions added to double- and triple-ζ basis sets, but none of these changes made much difference for the FC terms, in that the rms deviation generally falls between 0.49 and 0.55 Hz (with one exception, which is 6-311G(d), at 0.58 Hz). However, adding one set of p-functions on hydrogen is again helpful: it reduces the rms deviation from 0.52 Hz for 6-31G(d) to 0.49 Hz for 6-31G(d,p) and from 0.58 Hz for 6-311G(d) to 0.53 Hz for 6-311G(d,p).

In summary, it appears that, for the calculation of the dominant Fermi contact terms, the 6-31G(d,p) basis set is entirely adequate, provided that the 1s part of the basis set is

decontracted and augmented with additional compact functions, e.g., according to the procedure invoked by the "mixed" option in the Gaussian 09 program.

We will return and examine in more detail the question of whether the calculation of all four terms that contribute to the coupling of protons in organic molecules actually improves results compared to those obtained on the basis of only the Fermi contact terms below.

Geometry Reoptimization. We also explored whether it pays to reoptimize geometries with larger basis sets than 6-31G(d). We found that the calculated coupling constants generally change very little. The rms change in the calculated values is generally below 0.15 Hz, either for total calculated coupling constants or for the Fermi contact terms. The changes for the cc-pVDZ and aug-cc-pVDZ basis sets are slightly larger: 0.2−0.3 Hz. Correspondingly, the rms deviations from experiment occasionally change slightly as a result of geometry reoptimization, but no systematic improvement was noted. For instance, the rms deviation for B3LYP/cc-pVDZ calculations increases from 0.99 to 1.06 Hz upon reoptimization with this basis set, while that for B3LYP/aug-cc-pVDZ decreases from 1.00 to 0.91 Hz upon the same change in procedure. The changes are generally smaller for the other basis sets. If the "mixed" option is invoked, geometry reoptimization has even less of an effect on the rms deviation ($\leq$0.03 Hz change in all cases we examined). Even those small changes are, however, almost all in the direction that including geometry reoptimization degrades performance. Thus, we conclude that, generally, B3LYP/6-31G(d) geometries form an excellent basis for calculating proton coupling constants.

We must, however, point out that most of the molecules in our test set have little conformational freedom (which is why they were included in the first place[34]). On the other hand, the geometries of flexible molecules where nonbonded interactions prevail are sometimes poorly modeled by standard DFT methods. In such cases, it may be better to optimize geometries by a method such as MP2 or the recently developed double hybrid density functionals of Grimme et al. which model nonbonded interactions more faithfully.[45] An example of this situation is provided by *cis*-cinnamic acid, a molecule from the probe set which is predicted to be planar by B3LYP/6-31G(d), but undergoes significant twisting of the −CH=CH−COOH group upon reoptimization by the MP2 method, which in turn leads to significant improvement in the agreement between calculated and measured proton coupling constants.

Table 2 shows that, for the eight basis sets (beyond 6-31G(d)) where the effect of geometry reoptimization was investigated, the change in the rms deviation between experimental and calculated proton couplings for the test set, is insignificant. If one looks at how reoptimization with a larger basis set changes the couplings themselves, the rms change is generally below 0.15 Hz, either for Jtotal or for FConly calculations. The average changes for the cc-pVDZ and aug-cc-pVDZ basis set are slightly larger (ca. 0.3 Hz) which is due to a few large changes that invariably involve geminal coupling constants of protons on sp2 carbons, notably formaldehyde (2.48 Hz) and different substituted ethylenes (0.7−1.0 Hz deviation). While the data in Table 2 correspond to calculations with the "u+1s" option, the situation is essentially identical if that option is not invoked (see Table S2b in the Supporting Information).

Solvent Modeling. In our study on calculating chemical shifts,[18] we had found that modeling the solvent in which an NMR spectrum was taken significantly improves the results.

Table 2. Effect of Including Geometry Reoptimization with Larger Basis Sets on Calculated J_{H-H} Values for the Test Set[a]

basis set	Jtotal[b]		FC only[c]	
	Δrmsd[d]	rmsDiff[e]	Δrmsd[d]	rmsDiff[e]
6-31G(d,p) u+1s	0.00	0.03	0.00	0.03
6-311G(d,p) u+1s	0.02	0.12	0.01	0.12
6-311++G(d,p) u+1s	0.00	0.12	0.00	0.13
cc-pVDZ u+1s	−0.03	0.30	0.03	0.30
aug-cc-pVDZ u+1s	−0.03	0.28	0.00	0.29
cc-pVTZ u+1s	0.05	0.14	0.03	0.13
aug-cc-pVTZ u+1s	0.05	0.14	0.03	0.14

[a] Gas-phase calculations. [b] Calculation of total coupling constants. [c] Calculation of Fermi−Contact terms only. [d] Change in the rms deviation between experimental and calculated J_{H-H} for the test set: negative numbers are for an improvement, positive ones for a deterioration of the agreement. [e] rms difference between J_{H-H} calculated at the B3LYP/6-31G(d) geometry and that calculated at a geometry reoptimized with the basis set listed in the leftmost column (without the u+1s option).

Table 3. Effect of Including Solvent by SCRF Calculations on the Calculated J_{H-H} Values for the Test Set[a]

basis set	Jtotal[b]		FC only[c]	
	Δrmsd[d]	rmsDiff[e]	Δrmsd[d]	rmsDiff[e]
6-31G(d,p) u+1s	0.03	0.22	0.02	0.22
6-31+G(d,p) u+1s	0.04	0.22	0.04	0.22
6-311G(d,p) u+1s	0.03	0.24	0.03	0.24
6-311++G(d,p) u+1s	0.05	0.21	0.06	0.22
cc-pVDZ u+1s	0.02	0.17	0.00	0.17
aug-cc-pVDZ u+1s	0.04	0.17	0.03	0.17
cc-pVTZ u+1s	0.02	0.21	0.03	0.21
aug-cc-pVTZ u+1s	0.03	0.23	0.04	0.23

[a] Calculations at the gas-phase B3LYP/6-31G(d) geometries. [b] Calculation of total coupling constants. [c] Calculation of Fermi−Contact terms only. [d] Change in the rms deviation between experimental and calculated J_{H-H} for the test set: negative numbers are for an improvement, positive ones for a deterioration of the agreement. [e] rms difference between J_{H-H} calculated in the gas phase and in the presence of a simulated solvent.

We therefore also examined this question in the present context of calculating J_{H-H}, but we found no improvement on inclusion of a dielectric continuum corresponding to chloroform by SCRF calculations. This conclusion is illustrated by the data in Table 3, which lists the rms change in the coupling constants as a result of accounting for solvation for the test set, as well as the *change* in the rms deviation between experimental and calculated proton couplings. In fact, accounting for solvation does not change the calculated coupling constants by more than about 0.2 Hz on average, and consistently leads to a small *deterioration* of the agreement with experiment, at least if basis sets are augmented by additional core functions (if one does not do this, the results are less consistent).

Especially in FConly calculations this outcome is not surprising because the electron density at the nucleus is not expected to depend strongly on the environment. Tables 3 and S3 in the Supporting Information shows that, for the nine basis sets where the effect of solvent was investigated, the rms change in the calculated coupling constants themselves is consistently ca. 0.2 Hz, either in Jtotal or FConly, and whether or not geometry reoptimization (with SCRF) is carried out.

Again, we need to point out that there can be exceptional cases. The most notable one we have encountered is formaldehyde where the geminal coupling of the two protons (40.7 Hz in THF, the largest that appears in our test set) is predicted much more accurately if account is taken of the solvent (deviation 2.47 Hz in the gas phase, 1.07 Hz in THF in Jtotal calculations, 3.11 vs 1.69 Hz in FConly calculations, both with B3LYP/6-31G(d,p) u+1s basis set). However, this advantage disappears if one uses the linear scaling factors determined for the test set (deviation −0.11 Hz in the gas phase, −1.65 Hz in THF in Jtotal calculations, −0.76 vs −2.25 Hz, respectively, with FConly). Of course such a large coupling is extremely sensitive to small changes in the scaling factor, so one cannot really draw any conclusions from this case.

However, in general, it seems clear that the effects of geometry reoptimization and of solvent modeling are very small, especially when the basis set is augmented by additional core functions, and more often unhelpful than helpful. We therefore conclude that, in general, there is no reason not to evaluate J_{H-H} by gas phase calculations on gas-phase B3LYP/6-31G(d) geometries. Cases

where this general rule might not apply have been pointed out and such cases should be recognized and treated on an ad-hoc basis.

Fermi Contact Term vs Total Coupling Constant. While one would suppose that inclusion of all the terms that contribute to nuclear spin coupling in calculations of coupling constants ("Jtotal") should improve the agreement with experiment over calculations where only the FC contribution is accounted for ("FConly"), no one appears to have ever examined systematically to what extent this is actually true in calculations of J_{H-H}.

As we have pointed out previously, our calculations indicate that the results obtained by calculating only the FC terms, even with the modest 6-31G(d,p) basis set (rms deviation = 0.49 Hz) are actually better than those from the best calculations of all four terms, even if very large valence basis sets are employed (rms deviation = 0.53 Hz), provided that one decontracts and augments the core functions and applies linear scaling.

Figure 2 addresses the question raised by this observation in a more systematic fashion. It depicts all 251 computational methods that we tested, with the rms deviation for the FConly calculations on the vertical axis and the rms deviation for Jtotal calculations, using the same procedure, on the horizontal axis.

If linear scaling is applied to both sets of results, the conclusion is rather unambiguous: agreement with experiment *never* improves significantly but often decreases considerably as a result of including terms other than Fermi contact! This conclusion follows from the fact that, with a few minor exceptions, all the points in this plot either fall on the diagonal (FConly equally good as Jtotal) or below the diagonal (FConly superior to Jtotal). The only significant exception to this rule is marked by the filled circle (TPSSh/6-31G(d) u+1s), but even in this case the improvement is small (1.16 to 1.08 Hz), and ultimately irrelevant since much superior methods exist. If one compares the unscaled results (see Figure S2 in the Supporting Information), certain combinations of functionals and basis sets yield slightly better results for Jtotal than for FConly calculations. But then, linear scaling improves the results so much (for either type of calculations) that this observation is not of practical relevance.

One might also ask by how much the calculated total coupling constants and the Fermi contact terms differ from each other
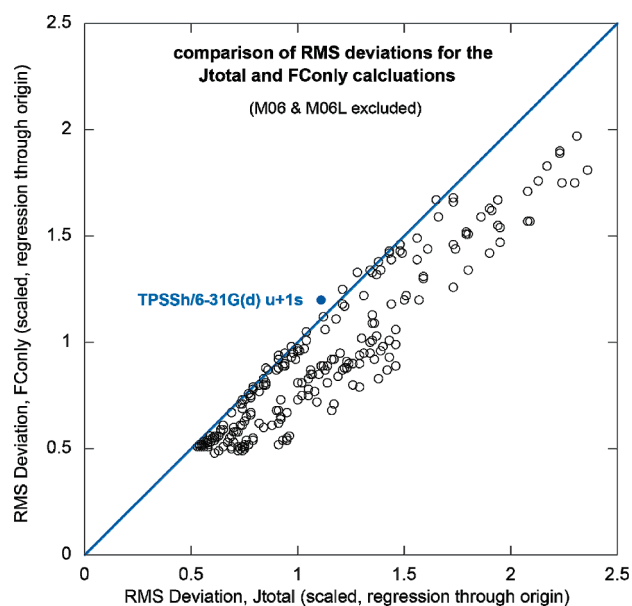
Figure 2. Comparison of the rms deviations between experimental and calculated total calculated coupling constant ("Jtotal") and the Fermi contact terms only ("FC only") for the entire test set, using the *scaled* computational results. Each point represents a level of theory. Points on the blue diagonal line represent methods of calculation that yield predictions of "Jtotal" and "FC" that match experiment equally well, after linear scaling. Points below the line represent methods of calculation for which the FC values match experiment more closely than do the Jtotal values. The only point which lies significantly above the line is shown as a solid blue circle. The 18 methods for which the rms deviation is greater than 2.5 Hz have been omitted from the plot.

(this difference being equal to the sum of the other terms). On average, the rms value of this difference is 0.32 Hz for all 251 methods, i.e., less than the rms difference between calculation and experiment for the best methods, with the largest deviation being 0.93 Hz. This shows that the contribution of the sum of the spin−orbit (SO) and spin-dipole (SD) terms to J_{H-H} is indeed minor in most cases.

Thus, we conclude that, in calculations of J_{H-H}, it is in fact best to ignore terms other than the Fermi contact term, probably because the accuracy with which these other terms can be computed, even with the largest basis sets examined in this study, is such that their sum cannot be predicted with sufficient exactitude to improve the results. Probably the empirical scaling factors that result from the linear scaling procedure of the calculated FC terms include some averaged correction for the missing SO and SD terms, in addition to corrections for other deficiencies of the methods. Note, however, that we do *not* claim that the same is true if one wants to predict couplings to other nuclei, where the methods to calculate the other terms may indeed prove useful.[46]

There is significant economy in considering only the FC terms, firstly because one can avoid the costly calculation of the other terms altogether, but also because ignoring them greatly reduces the stringency of basis set requirements. In the following section we will focus on the aspect of computational economy which is crucial when it comes to calculate large molecules and/or if one has to account for conformational averaging in flexible molecules.

Considerations of Computational Economy. With the above conclusions in hand, we examined what methods provide the best cost/performance ratio. To this end, we normalized the CPU times for running a set of calculations on our entire test set to that for doing a calculation with the 6-31G(d) basis set and with no extra options (no solvent, no geometry reoptimization, no basis set enhancement). Figure 3a shows that, for Jtotal calculations one generally needs to use triple-ζ basis sets to achieve good performance. The best method in this case is B3LYP/6-311G(3d,2p) u+1s (rms error = 0.53), but such calculations are ca. 12 times more expensive than similar calculations with the 6-31G(d) basis set. Other selected methods are highlighted in color in Figure 3a.

Figure 3b shows the same plot, this time if one considers only the Fermi contact terms. The two best methods in this case are B3LYP/cc-pVTZ/SCRF (rms deviation 0.48 Hz) and B3LYP/6-31G(d,p) u+1s (rms deviation 0.49 Hz). As calculations with the latter method take less than half the CPU time than those with the former, the choice is clear (Table 4). Very similar performance can be achieved, at a slightly higher cost, with the cc-pVDZ basis set (rms deviation = 0.50 Hz).

An interesting aspect of Figure 3 is that all modeling efforts seem to "hit a wall" at an rms deviation between calculated and measured J_{H-H} of ca. 0.5 Hz. We suspect that this is in part due to the fact that experimentally determining such small couplings is not always trivial: often, the accurate determination of coupling constants requires the actual simulation of complex patterns of lines, which is not always done. Also, couplings that involve magnetically equivalent protons are often determined from J_{H-D} which are 6.5 times smaller than J_{H-H} and are thus associated with a larger relative error. On the other hand, we neglect in our calculations effects due to vibrational averaging, and even the steepest Gaussian functions that are added to the core basis set cannot correctly model the cusps of s-functions at the nuclei, so that one has to rely to some extent on compensation of errors to arrive at good agreement between experiment and theory.

Improving Efficiency. In an effort to minimize the expense in CPU time that is needed to achieve good agreement with experiment, we examined options to improve the efficiency of the calculations. First we investigated whether tightening the SCF convergence, or increasing the grid for the integral calculations, as it is often recommended in the literature, is necessary in the case of proton couplings. In fact, we found no single case where converging the SCF to 10^{-10} h or using an ultrafine grid (two measures which together increase the cost of the calculation by a factor of about two!) changed any calculated J_{H-H} by more than 0.01 Hz. Thus, running calculations with the default grid and SCF-convergence is perfectly sufficient in calculations of proton coupling constants.

After we realized that FConly calculations give better results than Jtotal calculations, we sought ways to improve the computational efficiency of the former. First, if one is interested only in proton couplings, it would seem to suffice to calculate the FC terms at the protons, which in the Gaussian program is possible. But then it would also seem that uncontraction and augmentation of the core basis sets at other nuclei than H should not much affect the proton coupings. We examined these options, using our best and most economical method (B3LYP/6-31G(d,p) u+1s),[47] and found that, indeed, the calculated J_{H-H} change very little if one does not augment the core functions on other atoms. On the other hand, this modification results in a factor of almost six in CPU time
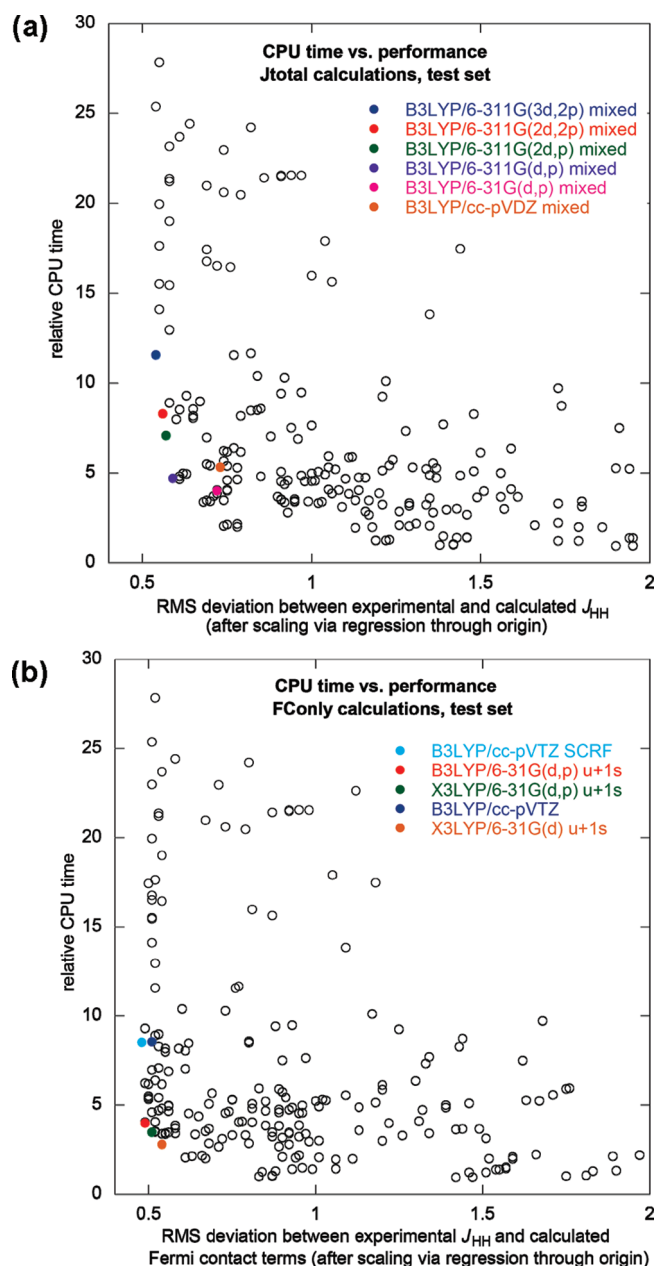
(a) CPU time vs. performance
Jtotal calculations, test set

● B3LYP/6-311G(3d,2p) mixed
● B3LYP/6-311G(2d,2p) mixed
● B3LYP/6-311G(2d,p) mixed
● B3LYP/6-311G(d,p) mixed
● B3LYP/6-31G(d,p) mixed
● B3LYP/cc-pVDZ mixed

relative CPU time

RMS deviation between experimental and calculated J_{HH}
(after scaling via regression through origin)

(b) CPU time vs. performance
FConly calculations, test set

● B3LYP/cc-pVTZ SCRF
● B3LYP/6-31G(d,p) u+1s
● X3LYP/6-31G(d,p) u+1s
● B3LYP/cc-pVTZ
● X3LYP/6-31G(d) u+1s

relative CPU time

RMS deviation between experimental J_{HH} and calculated
Fermi contact terms (after scaling via regression through origin)

Figure 3. (a) Comparison of CPU time and accuracy for the 251 methods tested for computing all four terms that contribute to the proton coupling constant. Accuracy is measured as the rms deviation between experiment and the scaled computed values. The CPU time variable is defined so that an unmodified B3LYP/6-31G(d) calculation on the entire test set corresponds to a CPU time of 1.0. The best methods are those in the lower left-hand corner of the plot. The legend hides three points; in addition, 21 points lie off the chart to the right (rms >2.0 Hz) (ten of these for M06 and M06L, ten for WP04, and one for VSXC), and another 21 points lie off the chart in the vertical direction, with relative CPU times greater than 30. The colored points in the plot show how the accuracy and the cost increase on improving the basis set. (b) Same comparison, but tested for computing the Fermi contact terms ("FConly"). Compare caption to Figure 3a. The legend hides four points; in addition, the 10 points for the M06 and M06L functionals lie off the chart to the right (rms >2.0 Hz), and another 20 points lie off the chart in the vertical direction, with relative CPU times greater than 30.

savings. Thus, to predict accurately J_{H-H} it is advantageous to calculate the FC terms and augment the 1s basis functions

Table 4. Methods Highlighted in Figure 3

basis set	method	rms[a]	slope[b]	CPU time[c]	mark in Figure 3
Jtotal (Figure 3a):					
6-311G(3d,2p) u+1s	B3LYP	0.54	0.91	11.6	blue
6-311G(2d,2p) u+1s	B3LYP	0.56	0.92	8.3	red
6-311G(2d,p) u+1s	B3LYP	0.57	0.92	7.1	green
6-311G(d,p) u+1s	B3LYP	0.59	0.92	4.7	purple
6-31G(d,p) u+1s	B3LYP	0.72	0.94	4.0	pink
cc-pVDZ u+1s	B3LYP	0.73	0.96	5.3	brown
FConly (Figure 3b):					
cc-pVTZ	B3LYP[d]	0.48	1.09	8.5	light blue
cc-pVTZ	B3LYP	0.51	1.10	8.5	dark blue
6-31G(d,p) u+1s	B3LYP	0.49	0.91	4.0	red
6-31G(d,p) u+1s	X3LYP	0.51	0.90	3.5	green
6-31G(d) u+1s	X3LYP	0.54	0.89	2.8	beige

[a] rms deviation between experimental and calculated coupling constants for the test set, after scaling by regression through the origin. [b] Slope for regression through the origin between experimental and calculated coupling constants for the test set. [c] CPU time, relative to B3LYP/6-31G(d), gas phase = 1.0. [d] Solvent modeled by an SCRF calculation.

Table 5. Factors That Improve Efficiency in Calculating J_{H-H}[a]

basis set	method[b] 1 2 3 4	RMSDE[c]	rmsd[d]	MaxD[e]	CPU time[f]
cc-pVTZ	A J A T	0.51			22.99
	N J A T	0.51	0.00	0.00	8.55
	N J A D	0.51	0.00	0.00	4.87
	N F A D	0.51	0.00	0.00	1.52
	N F H D	0.51	0.00	0.00	**1.04**
6-31G(d,p)	A J A T	0.49			**4.00**
	A J A D	0.49	0.00	0.00	1.79
	A F A D	0.49	0.00	0.01	1.36
	A J H D	0.49	0.00	0.01	1.05
	A F H D	0.49	0.00	0.01	0.82
	H F H D	**0.51**	**0.06**	**0.12**	**0.14**

[a] For gas phase, single-point calculations at the B3LYP/6-31G(d) geometries, for the entire test set. [b] Key for method: 1st character: A: u+1s *on all atoms* ("nmr=mixed" in G09), H: u+1s *only on H-atoms*, N = no change to the core basis sets; second character: J = calculate all components of J ("nmr=spinspin" in G09), F = calculate Fermi contact terms only ("nmr=FConly" in G09); third character: A = calculate coupling constants or Fermi contact terms *on all atoms* (default in G09), H = calculate *only on H-atoms* ("ReadAtoms"/H in G09); 4th character: T: tight criteria (scf(conver=10), integral(grid=ultrafine), as recommended in the Gaussian manual for calculations of NMR parameters), D = default criteria. [c] rms deviation with respect to experiment, for the test set. [d] Root mean square deviation relative to the top line of the block. [e] Maximum absolute deviation of calculated coupling constants (total or FConly), relative to the top line of the block. [f] Relative CPU time.

only on hydrogen atoms (we will denote this technique of "locally augmenting" the basis sets on H-atoms by the acronym "u+1s[H]")

Thus, we conclude that calculating the FC terms using the default convergence and grid parameters with the B3LYP functional and the 6-31G(d,p)u+1s[H] basis set provides the best

cost/performance ratio. Due to a fortuitous cancellation of errors, the results obtained without augmenting the basis set are of similar quality if one uses the cc-pVTZ basis set. However, with the above options implemented, such calculations are ca. eight times more expensive so we recommend this method only if decontracting and augmenting the basis sets on H-atoms is not an option (CPU time of 1.04 under optimal conditions on the scale used in Table 5, compared to 0.14). The FC terms obtained in this manner should be scaled by 0.9155.

Calculations on the Probe Set. As mentioned in the Methods section, an additional set of different molecules was set aside at the beginning to serve as a "probe set" for verifying the generality of the procedures identified as most promising based on performance with the test set. This probe set, which is shown in Scheme 2 and detailed in the Supporting Information, consists of 61 J_{H-H} values in 37 molecules, including some cases where conformational averaging is required, which was explicitly excluded in the test set.[34]

Eleven molecules in the probe set require averaging of non-equivalent positions in a methyl group (where the conformations are of course indistinguishable and of identical energy), while five required averaging between different conformations: methyl vinyl ether (*syn* and *anti*), acrylic acid (*s-cis* and *s-trans*), diethyl ether (*anti/anti* and *anti/gauche*), *trans*-cinnamic acid (*s-cis* and *s-trans*), and *cis*-cinnamic acid (*s-cis* and *s-trans*). The relative free energies of these conformations were evaluated with the B3LYP/6-31G(d) method that was used in all cases to optimize geometries. Averaging of proton NMR properties computed for discrete conformations has previously been shown to provide good agreement with experiment.[9,13]

The J_{H-H} values in the probe set were calculated in the gas phase with the B3LYP functional and the basis sets listed in Table 6 (which include decontraction and augmentation of the H(1s) basis set in every case except the last one). It is important to note that, while the calculated coupling constants and Fermi contact terms were scaled, it was by the slope parameters determined previously for the test set, *not* by new parameters determined for the probe set.

Figure 4 depicts the performance of our recommended procedure (B3LYP/6-31G(d,p) u+1s[H], gas-phase, FC terms scaled by 0.9155) on the probe set. The agreement between experiment and calculation is generally excellent, but three cases merit a brief discussion. The blue and red filled circles in Figure 4 represent the two cases where the discrepancy between calculation and experiment is greater than 1.25 Hz. (For all other cases, the discrepancy is less than 1.25 Hz.) These two cases are 1,2,3-butatriene[48] (2.04 Hz difference) and *cis*-cinnamic acid (1.51 Hz difference). The result for butatriene is disappointing, but perhaps not surprising, as the electronic structure of cumulenes is known to be difficult to model accurately by DFT.

The case of *cis*-cinnamic acid is more interesting. B3LYP/6-31G(d) calculations yield a planar geometry for this molecule, but MP2/6-31G(d) yields a geometry where the carbomethoxy-vinyl group is twisted out of the plane of the benzene ring by 35°. If this latter geometry is used, the calculated coupling constant drops from 13.8 to 12.9 Hz, which is in fact much closer to the experimental value of 12.3 Hz. The case of *cis*-cinnamic acid thus illustrates an important caveat: the procedures we recommend reproduce coupling constants well, provided one uses the correct geometry. B3LYP/6-31G(d) provides very good geometries, except in cases where dispersive (or steric) interactions,

Scheme 2. Set of Molecules (Not Included in the Scaling Procedure) Used To Probe Different Methods
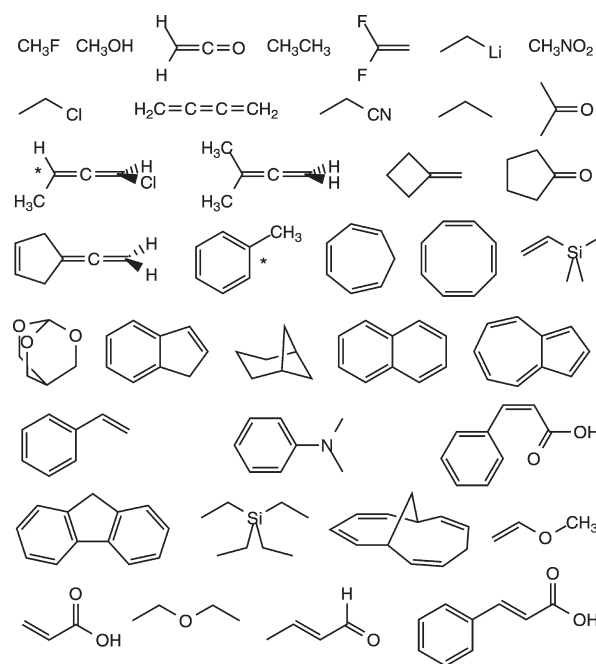

Table 6. Comparisons of Performance on the Probe Set and the Test Set[a]

basis set	test set		probe set		probe set, mod[b]	
	Jtotal[c]	FC[d]	Jtotal[c]	FC[d]	Jtotal[c]	FC[d]
6-31G(d) u+1s	0.91	0.52	0.89	0.55	0.83	0.46
6-31G(d,p) u+1s	0.72	0.49	0.73	0.56	0.64	0.47
6-31G(d,p) u+1s [H]		0.51		0.56		0.47
6-31G(d,3pd) u+1s	0.69	0.51	0.72	0.58	0.62	0.48
6-31+G(d,p) u+1s	0.75	0.50	0.76	0.55	0.69	0.47
6-311G(d,p) u+1s	0.59	0.53	0.66	0.59	0.56	0.50
6-311G(2d,2p) u+1s	0.56	0.53	0.66	0.60	0.56	0.51
6-311G(3d,2p) u+1s	0.54	0.52	0.65	0.59	0.55	0.51
6-311G(3df,3pd) u+1s	0.54	0.51	0.66	0.59	0.57	0.51
6-311++G(d,p) u+1s	0.60	0.55	0.69	0.60	0.60	0.52
6-311++G(df,2pd) u+1s	0.58	0.54	0.69	0.61	0.59	0.53
6-311++G(df,3pd) u+1s	0.58	0.53	0.69	0.60	0.59	0.52
6-311++G(2df,3pd) u+1s	0.55	0.52	0.67	0.60	0.57	0.52
6-311++G(3df,3pd) u+1s	0.53	0.51	0.66	0.59	0.57	0.51
cc-pVDZ u+1s	0.73	0.50	0.77	0.57	0.68	0.48
cc-pVTZ u+1s	0.56	0.51	0.67	0.59	0.58	0.50
cc-pVTZ	0.65	0.51	0.73	0.64	0.63	0.55

[a] rms differences versus experiment, for B3LYP calculations, gas-phase, at the B3LYP/6-31G(d) geometries. [b] Probe set with the two notable outliers eliminated: 1,2,3-butatriene and *cis*-cinnamic acid. [c] Calculation of total coupling constants. [d] Calculation of Fermi−Contact terms only.

which are not adequately modeled by DFT, strongly affect dihedral angles, as is the case in *cis*-cinnamic acid.

Cyclooctatetraene also represents a somewhat puzzling case. At first, it appeared that the discrepancy between experiment and
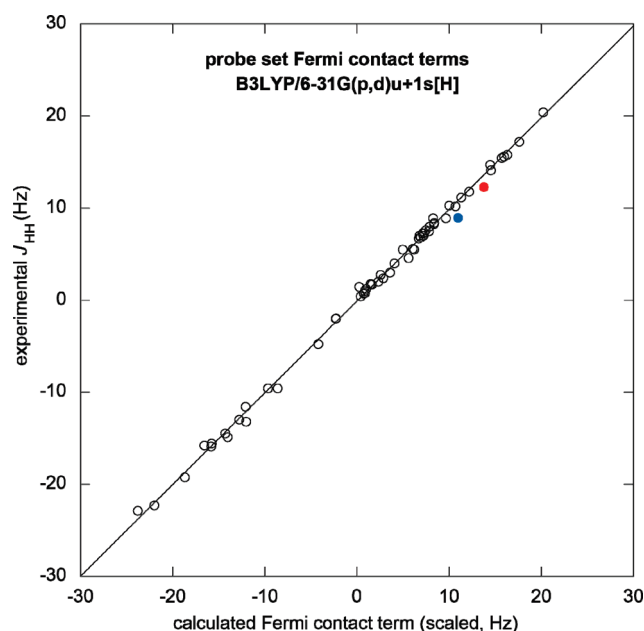
Figure 4. Plot of calculated Fermi contact terms (scaled by 0.9155) against the 61 experimental coupling constants from the probe set. The line drawn represents an unrestricted least-squares fit through the unfilled circles (r^2 = 0.998, slope = 0.996, intercept = −0.097 Hz). The solid blue circle represents 1,2,3-butatriene (8.95 Hz expt vs 10.90 Hz calcd) and the solid red circle represents *cis*-cinnamic acid (12.3 Hz expt vs 13.78 Hz calcd). These are the only two cases where the absolute error exceeds 1.25 Hz.

calculation exceeded 3 Hz. However, we had used a calculated average of the couplings across the single and double bonds, assuming that the bond shift isomerization is rapid. In fact, the experimental determination turns out to have been done at −50 °C, at which temperature this isomerization is slow, and the reported coupling of 11.8 Hz is claimed as being that across the double bond.[49] In fact, calculations predict 12.2 Hz for this coupling, which represents satisfactory agreement. It remains mysterious why the coupling across the single bond, calculated to be 4.9 Hz, has never been reported.[50] Nonetheless, we conclude that cyclooctatetraene does not, upon closer examination, represent a dramatic failure of the method.

Table 6 lists the performance on the probe set, in "Jtotal" and "FConly" calculations with different basis sets. If one excludes butatriene and uses the MP2 geometry of *cis*-cinnamic acid, the performance on the probe set closely parallels that on the test set. These results give us confidence that the performance and scaling factors reported for the test set are not bound to that particular choice of compounds, but instead apply more broadly to a wide variety of organic compounds.

The results on the test and probe sets taken together show that one can calculate J_{H-H} values quite efficiently and accurately using B3LYP/6-31G(d,p) u+1s[H] in the gas-phase, provided one uses correct geometries. In daily practice the latter caveat may constitute a problem, especially when there is conformational flexibility. Still, it is good to have assurance that that, if one can get the geometry right, the calculation of NMR properties will almost undoubtedly work well.

Practical Considerations. The goal of this work is to encourage regular practitioners of NMR spectroscopy not to hesitate to perform electronic structure calculations if these

Scheme 3. 1-Azabicyclo[3.2.0]heptane Stereoisomers Used To Test the B3LYP/6-31G(d,p) u+1s Method
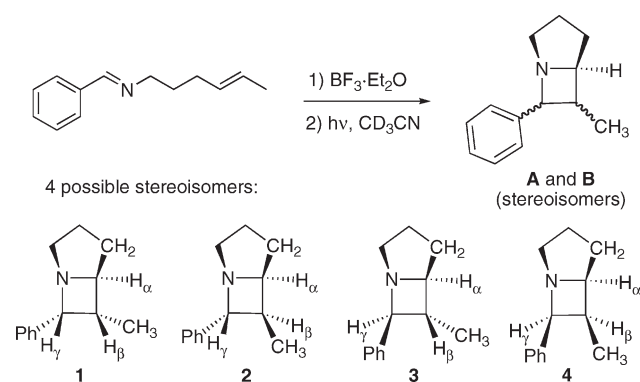
might help them in their interpretation of ^{1}H NMR spectra in cases where other methods, e.g., those based on additivity schemes, do not suffice. Experience suggests that the barriers that keep experimental chemists from engaging in such calculations are often of a purely practical nature. We have therefore made an effort to pave the way to obtaining useful results by providing a series of perl scripts that automate much of the process for users of the Gaussian program. One script extracts the molecular geometry from a geometry optimization output file. A second script uses this molecular geometry to create an input file for calculating chemical shifts and proton coupling constants according to our recommended procedures with the Gaussian program.

A third script extracts those values from the output of the calculation and arranges them in convenient tables. A fourth script offers the possibility to average the shifts and couplings for groups of protons that become equivalent through rapid averaging between *degenerate* conformations, such as, e.g., those of methyl groups. Finally, a fifth script allows calculation of Boltzmann-averaged chemical shifts and coupling constants for atoms that are made equivalent by conformational averaging between *different* conformations (i.e., conformations having different energies), from multiple files created by the third or fourth script.

With these tools,[51] which are described in detail in the Supporting Information, modeling ^{1}H NMR spectra does not require any special knowhow. In fact, MestreLab Research, Inc.,[52] has written a script which imports files created with our scripts directly into their Mnova program which thus makes it possible to simulate entire ^{1}H NMR spectra on the basis of calculated shifts and proton coupling constants.

To illustrate the utility of calculations of J_{H-H} we use an example from the recent research of a Fribourg graduate student who prepared 1-azabicyclo[3.2.0]heptanes by the method shown in Scheme 3.

By this method, she obtained two stereoisomeric products **A** and **B** and faced the problem of finding out which of them corresponded to which of the four possible stereoisomers **1**−**4** of the bicyclic amine.

Inspection of the ^{1}H NMR spectra of **A** and **B** revealed three characteristic protons, H_α, H_β, and H_γ, which might lend themselves to distinguish structures **1**−**4**. Thus, we subjected these four structures to the computational protocol outlined above and juxtaposed the coupling patterns of these three protons to the corresponding patterns in the experimental spectra of
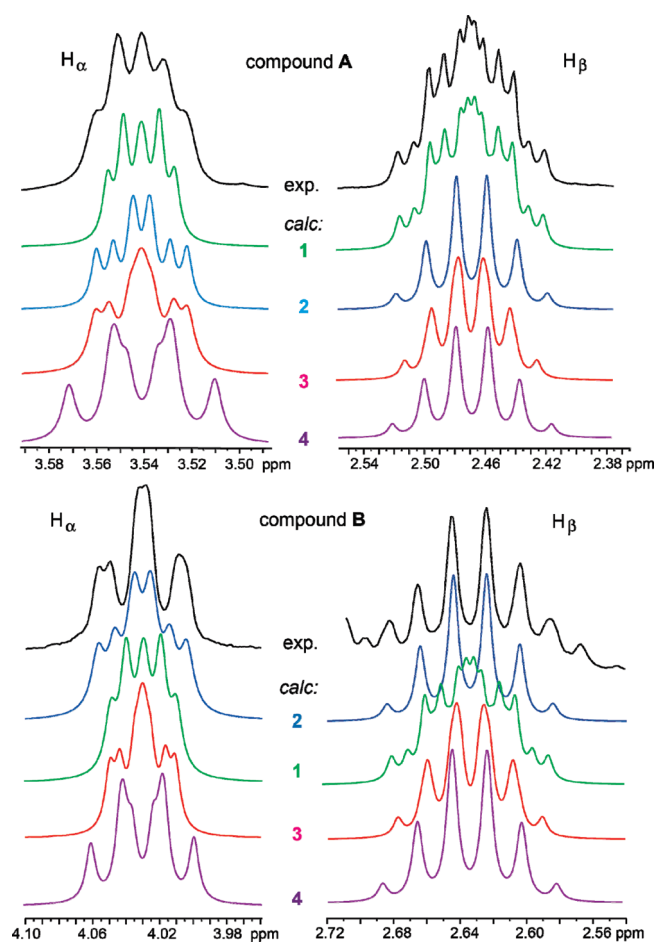
Figure 5. Experimental spectra for H_α and H_β in the bicyclic amines shown in Scheme 3 and simulations of the calculated coupling patterns for stereoisomers **1−4**.

A and **B**. Thereby, it became evident that H_γ is of limited help in distinguishing **1−4** because it is invariably a doublet with a coupling of 7−9 Hz (exp: **A**: 9.3 Hz, **B**: 7.7 Hz). However, H_α and H_β proved to be highly indicative, as shown in Figure 5, where we have aligned the centers of the simulated coupling patterns with those of the experimental bands (we could also have used the chemical shifts of the signals for the three protons to distinguish between the three stereoisomers, but as the differences between experiment and calculation are usually larger than the width of the bands a direct comparison would have been more difficult. The full data are given in the Supporting Information).

In compound **A**, the signal for H_β (upper right) is modeled quite well by the simulation based on the computational results for **1** (green trace) whereas the coupling patterns predicted for the other three stereoisomers are in much better qualitative accord with that observed for compound **B** (lower right). However, these three coupling patterns are all qualitatively similar sextets, so they do not permit an unambiguous distinction between **2−4** with regard to the assignment of compound **B** (although we note that the simulation for **2**, blue trace, is in better quantitative accord with the signal for H_β in **B** that those for **3** and **4**).

Conversely, the assignment of **B** is less ambiguous based on the simulations for H_α (lower left), where that for stereoisomer **2** is in significantly better accord with the observed band shape than those for the other stereoisomers (although **3** cannot be rigorously

excluded). Finally, returning to compound **A**, we note that the assignment obtained above with H_β is confirmed by the good accord of the experimental pattern for H_α with that calculated for **1**.

It is gratifying to note that the above assignments of **A** to stereoisomer **1** and **B** to **2**, based exclusively on quantum chemical calculations of J_{H-H}, were confirmed by NOE-measurements which clearly indicated a proximity of H_α to the methyl group and of H_β to H_γ in compound **A**, while in compound **B** H_α and H_β are proximal and H_γ is close to the methyl group.

■ CONCLUSION

The performance of 250 different computational protocols (combinations of density functionals, basis sets and methods) was assessed on a set of 165 well-established experimental $^1H-^1H$ nuclear coupling constants (J_{H-H}) from 65 molecules spanning a wide range of "chemical space". Thereby, we found that, if one decontracts and augments basis sets on H with compact 1s functions, and if one allows for linear scaling of the raw results, calculations of only the Fermi contact term actually yield more accurate predictions than calculations where all four terms that contribute to J_{H-H} are evaluated, presumably because the sum of these other terms cannot be calculated with sufficient accuracy to improve the overall result.

In fact, it turns out that B3LYP/6-31G(d,p) u+1s is equal in performance to the best methods tested, yielding predictions of J_{H-H} with a root-mean-square deviation from experiment of less than 0.5 Hz for our test set, and is in addition quite economical. A selection of the better methods was tested on a probe set comprising 61 J_{H-H} values from 37 molecules. In this set, we also included five molecules where conformational averaging is required. The rms deviations were better or equal than those with the training set which indicates that the method we recommend is robust and generally applicable for organic molecules.

In the Supporting Information we provide detailed instructions on how to carry out calculations of ^1H chemical shifts and J_{H-H} most economically and provide scripts to extract the relevant information from the outputs of calculations with the Gaussian program in clearly arranged form, e.g., to feed them into programs for simulating entire ^1H NMR spectra.

■ ASSOCIATED CONTENT

S **Supporting Information.** (a) Full reference to the Gaussian program. Description of the scripts mentioned in the section "Practical Consideration", complete test set and probe set, with references to the source of the experimental information. Additional Figures S1−S3 and Tables S2−S4 referred to in the text. (b) Zip archive containing (i) Excel master spreadsheets for the test set and the probe set (ii) the scripts described in (a), (iii) text files with Cartesian coordinates and total energies for all compounds in the test set and the probe set, and (iv) full tabulations of results for each method examined, both for the test set (333 concatenated tables) and for the probe set (32 tables). This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Authors
*E-mail: thomas.bally@unifr.ch, prablen1@swarthmore.edu.

Notes
[†]Part 1: Jain, R.; Bally, T.; Rablen, P. R. *J. Org. Chem.* **2009**, *74*, 4017.

■ REFERENCES

(1) Günther, H., *NMR Spectroscopy: Basic Principles, Concepts and Applications in Chemistry*, 2nd ed; John Wiley & Sons: New York, 1995;

(2) Bifulco, G.; Dambruoso, P.; Gomez-Paloma, L.; Riccio, R. *Chem. Rev.* **2007**, *107*, 3744.

(3) Helgaker, T.; Jaszuński, M.; Ruud, K. *Chem. Rev.* **1999**, *99*, 293.

(4) Bagno, A. *Chem.—Eur. J.* **2001**, *7*, 1652.

(5) Bagno, A.; Saielli, G. *Theor. Chem. Acc.* **2007**, *117*, 603.

(6) Krivdin, L. B. *H. C. R. Ann. Rep. NMR Spectrosc.* **2007**, *61*, 133.

(7) Helgaker, T.; Jaszuński, M.; Pecul, M. *Prog. Nucl. Magn. Reson. Spectrosc.* **2008**, *53*, 249.

(8) Kaupp, M.; Bühl, M., Malkin, V. G., Eds.; *Calculation of NMR and EPR Parameters*; Wiley-VCH: Weinheim, 2004. See in particular Chapter 7 by Helgaker and Pecul on the calculation of spin—spin coupling constants (pp 101 ff.)

(9) Bagno, A.; Rastrelli, F.; Saielli, G. *Magn. Reson. Chem.* **2008**, *46*, 518.

(10) Bifulco, G.; Bassarello, C.; Riccio, R.; Gomez-Paloma, L. *Org. Lett.* **2004**, *6*, 1025.

(11) Di Micco, S.; Chini, M. G.; Riccio, R.; Bifulco, G. *Eur. J. Org. Chem.* **2010**, 1411 and references cited therein.

(12) Katritzky, A. R.; Akhmedov, N. G.; Doskocz, J.; Hall, C. D.; Akhmedova, R. G.; Majumder, S. *Magn. Reson. Chem.* **2007**, *45*, 5.

(13) Mendoza-Espinoza, J. A.; López-Vallejo, F.; Fragoso-Serrano, M.; Pereda-Miranda, R.; Cerda-García-Rojas, C. *J. Nat. Prod.* **2009**, *72*, 700.

(14) Merrick, J.; Moran, D.; Radom, L. *J. Phys. Chem. A* **2007**, *111*, 11683.

(15) Petrovic, A. G.; Navarro-Vázquez, A.; Alonso-Gómez, J. *Curr. Org. Chem.* **2010**, *14*, 1612 and references cited therein.

(16) Poza, J. J.; Jimenéz, C.; Rodriguez, J. *Eur. J. Org. Chem.* **2008**, 3960.

(17) Smith, S. G.; Goodman, J. M. *J. Am. Chem. Soc.* **2010**, *132*, 12946 and references cited therein.

(18) Jain, R.; Bally, T.; Rablen, P. R. *J. Org. Chem.* **2009**, *74*, 4017.

(19) Karplus, M. *J. Am. Chem. Soc.* **1963**, *85*, 2870.

(20) Houseknecht, J. B.; Altona, C.; Hadad, C. M.; Lowary, T. L. *J. Org. Chem.* **2002**, *67*, 4647 and references cited therein.

(21) It is this perturbation which is responsible for the transmission of the information on the magnetic moment of a given nucleus to the other nuclei and thus leads to the coupling of the nuclear spins.

(22) Lantto, P.; Vaara, J.; Helgaker, T. *J. Chem. Phys.* **2002**, *117*, 5998.

(23) Lutnæs, O. B.; Helgaker, T.; Jaszuński, M. *Mol. Phys.* **2010**, *108*, 2579.

(24) Helgaker, T.; Lutnæs, O. B.; Jaszuński, M. *J. Chem. Theor. Comput.* **2007**, *3*, 86.

(25) Jensen, F. *J. Chem. Theor. Comput.* **2006**, *2*, 1360.

(26) Helgaker, T.; Jaszuński, M.; Ruud, K.; Górska, A. *Theor. Chem. Acc.* **1998**, *99*, 175.

(27) Lutnæs, O. B.; Ruden, T. A.; Helgaker, T. *Magn. Reson. Chem.* **2004**, *42*, S117.

(28) Deng, W.; Cheeseman, J. R.; Frisch, M. J. *J. Chem. Theory Comput.* **2006**, *2*, 1028.

(29) Frisch, M. J. et al. Gaussian09, Revision A.02; Gaussian, Inc.: Wallingford, CT, 2009 (full reference is given in the Supporting Information).

(30) Krivdin, L. B. *Magn. Reson. Chem.* **2004**, *42*, S168 and references cited therein.

(31) Ruden, T. A.; Lutnæs, O. B.; Helgaker, T.; Ruud, K. *J. Chem. Phys.* **2003**, *118*, 9572.

(32) Yachmenev, A.; Yurchenko, S. N.; Paidarova, I.; Jensen, P.; Thiel, W.; Sauer, S. P. A. *J. Chem. Phys.* **2010**, *132*, 114305 and references cited therein.

(33) Ruden, T.; Helgaker, T.; Jaszuński, M. *Chem. Phys.* **2004**, *296*, 53.

(34) We are perfectly aware of the fact that many molecules that practicing organic chemists face every day show some conformational flexibility. To properly account for this requires accurate relative free energies of different conformations, which constitutes a compounding factor that we wanted to exclude from our present analysis.

(35) Jackman, L. M.; Sternhell, S., *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry*, 2nd ed.; Pergamon Press: New York, 1969;

(36) Crews, P.; Rodriguez, J.; Jaspars, M. *Organic Structure Analysis*; Oxford University Press: New York, 1998.

(37) Gordon, A. J.; Ford, R. A., *The Chemist's Companion: A Handbook of Practical Data, Techniques, and References*. Wiley: New York, 1972;

(38) See, e.g., http://cccbdb.nist.gov/vibnotes.asp (accessed 1/25/2011).

(39) Ochsenfeld, C.; Kussmann, F.; Koziol, F. *Angew. Chem., Int. Ed.* **2004**, *43*, 4485.

(40) This situation differs from that for chemical shifts, where a nonzero intercept reflects the fact that a chemical shift always represents a difference in magnetic shielding relative to some standard. Coupling constants, on the other hand, are absolute quantities, not referenced to a standard.

(41) Wiitala, K. W.; Hoye, T. R.; Cramer, C. J. *J. Chem. Theor. Comput.* **2006**, *2*, 1085 In Gaussian, the WP04 functional is invoked by specifying the BLYP keyword and adding iop (3/76 = 1000001189, 3/77 = 0961409999, 3/78 = 0000109999) to the keyword line.

(42) Bagno, A.; Rastrelli, F.; Saielli, G. *Chem.—Eur. J.* **2006**, *12*, 5514.

(43) Other workers have also based predictions of proton coupling constants on calculated FC terms alone, albeit with special basis set, decontracted and augmented on H-atoms: Diéz, E.; Casanueva, J.; San Fanian, J.; Esteban, A. L.; Galache, M. P.; Barone, V.; Peralta, J. E.; Contreras, R. H. *Mol. Phys.* **2005**, *103*, 1307.

(44) Zhao, Y.; Truhlar, D. G. *Acc. Chem. Res.* **2007**, *41*, 157.

(45) Schwabe, T.; Grimme, S. *Acc. Chem. Res.* **2008**, *41*, 569.

(46) Indeed, it has been established that for C—H coupling constants, it is at least sometimes important to include terms other than the Fermi contact term: Bagno, A.; Rastrelli, F.; Saielli, G. *J. Phys. Chem. A.* **2003**, *107*, 9964–9973.

(47) We also investigated B3LYP/6-311G(d,p)u+1s and B3LYP/cc-pVTZ u+1s in this manner; full details appear in the Supporting Information

(48) 1,2,3-Butatriene has both a *cis* and a *trans* coupling, but the two are extremely similar, and only an averaged value is available from experiment.

(49) Anet, F. A.; Schlenk, G. E. *J. Am. Chem. Soc.* **1971**, *93*, 556.

(50) Naor, R.; Luz, Z. *J. Chem. Phys.* **1982**, *76*, 5662.

(51) The group of Tantillo at UC Davies has set up a website called "Chemical Shift Repository" (CHESHIRE) where these scripts, including updated versions, are posted. See: http://cheshirenmr.info.

(52) http://mestrelab.com/ (accessed 2/5/2011).